

REMARKS UNDER 37 CFR § 1.116

Formal Matters

Claims 104-108, 121, 123, 127-135, and 142 are now pending in this application, following the present amendments.

Claim 104 has been amended to more particularly point out and distinctly claim the invention. The amendment to the claim was made solely in the interest of expediting prosecution, and is not to be construed as an acquiescence to any objection or rejection of any claim.

Support for the amendments may be found in the specification on page 32, line 22 to page 33, line 10, as originally filed. As such, no new matter is added by the amendments.

Please replace claim 104 with the clean version provided above.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Interview summary

Applicants wish to extend their gratitude to Examiner Huynh for the courtesy of allowing an interview with Applicants' representative, James S. Keddie, on November 6, 2002.

Potential claim amendments, the Statement of Availability, the ATCC catalog entry for 293 cells, and arguments for response were discussed.

Examiner Huynh suggested that amending claim 104 from "binds to all of human, mouse and rat connective tissue growth factors" to "binds to human, mouse and rat connective tissue growth factors" may remove some issues.

The Response in General

Claims have been rejected for lack of enablement and lack of written description.

Applicants have provided an enabling disclosure for what they are claiming and have adequately described what they are claiming. Specifically, applicants have provided detailed methods of how to make the claimed antibodies, and have provided working examples of at least 9 claimed antibodies. All one of skill in the art would have to do to make hundreds or more of the claimed antibodies is perform the described methods. Since the production of hundreds more of the claimed antibodies is well within the ability of one of skill in the art using the methods in the specification, and because a representative number of examples of this genus are described in the specification, the rejections should be withdrawn.

To the extent a further discussion is believed necessary, the Examiner is respectfully referred to the following.

Rejections under 35 U.S.C. § 112, First Paragraph

Enablement:

Claims 104-108, 121, 123, 127-135 and 142 were rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was not described in such a way as to enable one of skill in the art to make and use the invention. Specifically, the Office Action asserts that the specification does not provide any guidance as how to make and use the subject antibodies and, as such, the specification as filed fails to enable one skill in the art to practice the invention without undue experimentation. The Office Action further asserts that because the antibodies are not enabled by the specification, the subject labeled antibody, kits and insoluble carriers are also not enabled by the specification.

The law is clear that “[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.”¹ The Office is reminded that extensive experimentation may be performed, so long as the experimentation is routine, and that every species within a genus does not have

¹ *United States v. Teletronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). *See also, Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

to be operative for a claim to be fully enabled.

The Applicants respectfully submit that the specification and the amended claims, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation.

Statement of Availability

The Office indicates that deposit of hybridomas FERM BP-6208 and FERM BP-6209, and the 293-T cell line are required to satisfy the enablement requirement of claims 105-108, 127 and 155.

A "Statement of Availability" is attached hereto acknowledging the deposit criteria noted by the Examiner. Also, applicants have attached a copy of a catalog that shows details of the cell line available from ATCC. This copy serves as clear and convincing evidence that the 293-T cell line is "readily available to the public" as required by 37 CFR 1.802(b). The catalog details are available from the ATCC web site below.

<http://phage.atcc.org/cgi-bin/searchengine/longview.cgi?view=ce,691450,CRL-1573&text=CRL-1573>

Since the deposit has been made under the terms of the Budapest Treaty, claims directed to these deposits, e.g. claims 108 and 127 should be considered enabled.

The specification provides sufficient of guidance

The Office Action asserts that the specification does not provide any guidance as to how to make and use antibodies that bind to the mouse, human and rat CTGF.

Applicants have provided at least 9 working examples of IgG isotype non-human monoclonal antibodies that bind to human, mouse and rat CTGFs. Namely, as in Fig.1 of the present application, at least 8-64-6 (FERM BP-6209), 8-86-2 (FERM BP-6208), 8-97-3, 8-149-3, 15-38-1, 17-132, 24-53, 24-67 and 2-228-1 are examples of monoclonal antibodies that have this characteristic. A total of 5 monoclonal antibodies of this group of 9 CTGF binding non-human monoclonal antibodies inhibit the binding of human CTGF to human kidney-derived fibroblast cell line 293-T (i.e., 8-64-6, 8-86-2, 8-149-3, 17-132 and 2-228-1). As such, one of skill in the art, in order to produce, for example, hundreds of monoclonal antibodies that bind to human, mouse and rat CTGF would merely have to repeat the protocol, as described in detail in Example 4 (<4-1> through <4-13-3>), on pages 74-89 of the specification. As such, since the specification provides several working examples of subject monoclonal antibodies and has

provided detailed guidance on how to produce more of such monoclonal antibodies, such antibodies would be made and used without any undue experimentation.

In this respect it is notable that a sufficient number of the non-human monoclonal antibodies produced by the methods described in Example 4 (<4-1> through <4-13-3>) bind to human, mouse and rat CTGF, and further that most of these antibodies have an inhibitory effect on the binding of CTGF and 293-T cells.

Antibody production is a mature art

Furthermore, Applicants assert that antibody production, in general, is a mature art in which the levels of unpredictability are low.

Since their groundbreaking work on monoclonal antibody production by Köhler & Milstein in 1975, this art has advanced to such a point that antibodies are produced by one of skill in the art using very routine methodologies (for example, see Harlow et al., *Antibodies: A Laboratory Manual*, First Edition (1988) Cold Spring Harbor, N.Y.). In fact, the "Synopsis of Application of Written Description Guidelines" (hereafter "Synopsis"; posted on the USPTO world wide website on March 1, 2000) supports this assertion. With respect to antibodies, the Synopsis states, on page 60, that "This is a mature technology where the level is high and advanced".

As such, since antibody production is a mature art, one of skill in the art needs little guidance in practicing these methods.

The specification provides an enabling disclosure for "a portion of" a monoclonal antibody

The Office Action has stated that there is insufficient guidance as to which portion of a non-human monoclonal can inhibit the binding of human CTGF to 293 cells.

Portions of an antibody are very well understood by one of skill in the art to mean antibodies that are fragments of a full length antibody that still retain binding activity. In these cases the constant domain is usually at least partially deleted, thus leaving an antibody fragment that can still bind antigen. Making such antibodies (e.g. deleting certain amino acids from a full length antibody) is very well understood in the art, and is described in the specification on page 32, line 22 to page 33, line 10. Further working examples of fragments of subject monoclonal antibodies are provided in Example 8, on page 103 line 29

to 104 line 24.

Solely for the interest of expediting prosecution, applicant amended pending claim 104 so as to more particularly point out "a portion" invention under the above support in the present application as originally filed.

As such, in contrast to the assertions of the Office Action, the specification provides significant guidance as to a "portion" of a monoclonal antibody and would make such an antibody with no undue experimentation.

Summary of response to enablement rejection

Figures 1 of the specification show many of the non-human monoclonal antibodies that binds to CTGF of one mammalian species (e.g. human) will bind to a CTGF of other mammalian species (e.g. mouse or rat) and that most of these cross-reactive antibodies inhibit binding of CTGF and 293-T cells. This knowledge, coupled with the detailed methods for producing a CTGF-binding monoclonal antibody provided in the specification, would undeniably allow one of skill in the art make and use the claimed antibodies without undue experimentation. Applicants further assert that since the subject antibodies are fully enabled by the specification, the subject labeled antibody, kits and insoluble carriers are also fully enabled.

Applicants assert that the invention can be practiced by one of skill in the art without undue experimentation, and, as such, the rejection of these claims under 35 U.S.C. § 112, first paragraph (enablement) may be withdrawn.

Written Description:

Claims 104-108, 121, 123, 127-135 and 142 were further rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was not described in such a way as to convey possession of the claimed invention. Specifically, the Office Action asserts that the specification only discloses two monoclonal antibodies that cross-react with human, mouse and rat CTGF and further asserts that the specification fails to provide a representative number of species to describe genus.

Applicants respectfully traverse this rejection.

"Connective tissue growth factor" in the subject claims

In advance of detailed traversal below, applicants make clear the "Connective tissue growth factor (CTGF)" recited in the claims. The examiner states as below on page 7, lines 30 to page 8, line 1 of the outstanding office action.

" However, the amended claims still read on any non-human monoclonal antibody or portion thereof which (a) that binds to and (b) has IgG isotype where connective tissue growth factor is any CTGFs such as TGFbeta, PDGF, FGF, and EGF." (emphasis added)

The "CTGF" to which the subject monoclonal antibodies bind is the CTGF as defined on page 18, line 6 to page 19, line 25 of the present application and not TGFbeta, PDGF or EGF. CTGF is different molecule from any of the TGFbeta, PDGF or EGF.

The Written Description Guidelines indicate that such the subject claims are adequately described

The "Synopsis of Application of Written Description Guidelines" (hereafter "Synopsis"; posted on the USPTO world wide website on March 1, 2000), to which Examiners of the USPTO must adhere, describes an example (Example 16) similar to that of the Applicants.

The specification of this example discloses a purified 55kDa polypeptide and contemplates but does not teach an antibody that specifically binds to this polypeptide. In this example the claim "An isolated antibody capable of binding to antigen X" is made and even without a working example. The guidelines state that "The disclosure meets the requirement under 35 USC 112 first paragraph as providing an adequate written description of the claimed invention."

In the instant case, the applicants have provided a purified antigen (e.g. rat, human or mouse CTGF) and further have provided several working examples of monoclonal antibodies that bind to the antigen. When viewed using the reasoning presented by these Guidelines, the subject matter of the instant claims is adequately described in the specification.

The specification provides a sufficient number of species to describe the genus

The Office also asserts that the specification fails to describe additional representative species of non-human monoclonal antibodies that bind to CTGF, and that one of skill in the art would reasonably conclude that the specification fails to provide a representative number of species to describe the genus.

As noted above, applicants have provided at least 9 working examples of IgG isotype non-human monoclonal antibodies which bind to human, mouse and rat CTGFs. Namely, as in Fig.1 of the present application, at least 8-64-6 (FERM BP-6209), 8-86-2 (FERM BP-6208), 8-97-3, 8-149-3, 15-38-1, 17-132, 24-53, 24-67 and 2-228-1 have this characteristic. A total of 9 of this group of the 9 non-human monoclonal antibodies inhibit the binding of human CTGF to human kidney-derived fibroblast cell line 293-T (i.e., 8-64-6, 8-86-2, 8-149-3, 17-132 and 2-228-1). As such, a relatively sufficient number of claimed monoclonal antibodies are disclosed in the specification.

Because a relatively sufficient number of claimed monoclonal antibodies are disclosed, Applicants assert that a representative number of species of the claimed genus is described and, as such, one of skill in the art would recognize that the genus is adequately described.

The specification adequately describes "portions" of antibodies

The Office Action has stated that there is insufficient description of portions of a non-human monoclonal antibody can inhibit the binding of human CTGF to 293-T cells.

As respectfully mentioned above, portions of an antibody are very well understood by one of skill in the art to mean antibodies that are fragments of a full length antibody that still retain binding activity. In these cases the constant domain is usually at least partially deleted, thus leaving an antibody fragment that can still bind antigen. Making and using such antibodies (e.g. deleting certain amino acids from a full length antibody) is very well understood in the art, and such antibodies are described in the specification on page 32, line 22 to page 33, line 10. Further working examples of fragments of subject monoclonal antibodies are provided in Example 8, on page 103 line 29 to 104 line 24.

Solely for the interest of expediting prosecution, applicant amended pending claim 104 has been amended to more particularly point out "a portion" invention under the above support in the present application as originally filed.

As such, in contrast to the assertions of the Office Action, the specification provides significant description of portions of monoclonal antibodies.

Summary of response to written description rejection

In summary, Applicants assert that one of skill in the art would recognize that at least 9 working examples of non-human monoclonal antibodies that bind human, mouse and rat CTGFs, and at least 5 working examples of the 9 non-human monoclonal antibodies that inhibit the binding of human CTGF 293-T cells are adequate representations of the claimed genera, especially in light of the USPTO Guidelines which indicate that not even one example is actually needed. Applicants further assert that since the subject antibodies are adequately described, the subject labeled antibody, kits and insoluble carriers are also adequately described.

As such, the specification provides adequate description of the subject matter encompassed by the claims and the rejection may be withdrawn.

Conclusion

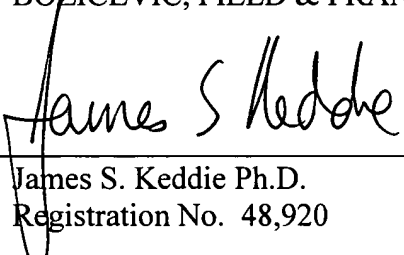
Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number SHIM006.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 11-08-2002

By: _____


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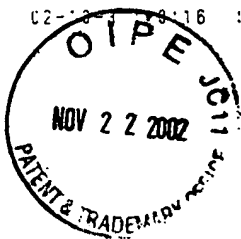
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claim 104 is amended, as shown below.

104. (Thrice Amended) A non-human monoclonal antibody or a portion thereof selected from the group consisting of F(ab')₂, Fab, Fab', Fv, sFv, dsFv and dAb, which (a) binds to ~~all of~~ human, mouse and rat connective tissue growth factors (CTGFs) and (b) has the IgG isotype.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Tamatani et al.
Title: Monoclonal Antibody Against Connective Tissue Growth Factor and Medicinal Uses Thereof
Appl. No.: 09/582,337
Filing Date: September 18, 2000
Examiner: P. Huynh
Art Unit: 1644
Atty. Docket No.: SHIM-006

STATEMENT OF AVAILABILITY

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Teruo Daito, Director of Intellectual property, of Japan Tobacco, Inc., declare:

1. A deposit of hybridoma clones 8-86-2 and 8-64-6 has been made and accepted under the provisions of the Budapest Treaty at the National Institute of Bioscience and Human Technology at the Agency of Industrial Science and Technology, the Ministry of International Trade and Industry of 1-1-3, Higashi, Tsukuba, Ibaraki, 305, Japan for patent purposes and assigned the following reference numbers FERM BP-6208 and FERM BP-6209, respectively;
2. All restrictions on the availability to the public of the culture deposited will be irrevocably removed upon the granting of a patent from the above-identified application;
3. The deposit will be maintained for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent, whichever is longer.

4. The deposit will be replaced if viable samples cannot be dispensed by the depository; and
5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued therefrom;

Further declarant sayeth not.

Signed this 30 day of October 2002

Signature:

Teruo Dalto

Printed Name:

Teruo Dalto

**ATCC**

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CRL-1573

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Cell Lines	
ATCC Number:	CRL-1573 order this item
Organism:	<i>Homo sapiens</i> (human)
Designation:	293
Depositors:	F.L. Graham
Tissue:	kidney; transformed with adenovirus 5 DNA
Tumorigenic:	yes. Tumors developed within 21 days at 100% frequency (5/5) in nude mice inoculated subcutaneously with 10(7) cells. [RF32725]
Receptors Expressed:	vitronectin
Morphology:	epithelial
Comments:	<p>The 293 cell line is a permanent line of primary human embryonal kidney transformed by sheared human adenovirus type 5 (Ad 5) DNA. [RF32725]</p> <p>The cells express the transforming gene of adenovirus 5.</p> <p>Although an earlier report suggested that the cells contained Adenovirus 5 DNA from both the right and left ends of the viral genome [RF32764], it is now clear that only left end sequences are present. [RF50113]</p> <p>The line is excellent for titrating human adenoviruses.</p> <p>The cell line does not adhere to the substrate when left at room temperature for any length of time, therefore, live cultures may be received with the cells detached.</p> <p>The cells will re-attach to the flask over a period of several days in culture at 37C.</p> <p>The cells express an unusual cell surface receptor for vitronectin composed of the integrin beta-1 subunit and the vitronectin receptor alpha-v subunit. [RF33793]</p> <p>Purified DNA from this line is available as ATCC 45504 (25 micrograms) and ATCC 45505 (100 micrograms).</p> <p>The Ad5 insert was cloned and sequenced, and it was determined that a colinear segment from nts 1 to 4344 is integrated into chromosome 19 (19q13.2). [RF50113]</p>
Age Stage:	fetus
Growth Properties:	adherent
Virus Susceptibility:	very sensitive to human adenoviruses [RF32725]
Karyotype:	<p>This is a hypotriploid human cell line. The modal chromosome number was 64, occurring in 30% of cells. The rate of cells with higher ploidies was 4.2 %.</p> <p>The der(1)t(1;15)(q42;q13), der(19)t(3;19)(q12;q13), der(12)t(8;12)(q22;p13), and four other marker chromosomes were common to most cells. Five other markers occurred in some cells only. The marker der(1) and M8 (or Xq+) were often paired.</p> <p>There were four copies of N17 and N22. Noticeably in addition to three copies of X chromosomes, there were paired Xq+, and a single Xp+ in most cells.</p>
Subculturing:	<p>Remove medium, and rinse with 0.25% trypsin, 0.03% EDTA solution. Remove the solution and add an additional 1 to 2 ml of trypsin-EDTA solution. Allow the flask to sit at room temperature (or at 37C) until the cells detach.</p> <p>Add fresh culture medium; aspirate and dispense into new culture flasks.</p>
Split Ratio:	A subcultivation ratio of 1:2 to 1:4 is recommended
Fluid Renewal:	Every 2 to 3 days
Freeze Medium:	culture medium 95%; DMSO, 5%
DNA Profile (STR):	<p>Amelogenin: X</p> <p>CSF1PO: 11,12</p> <p>D13S317: 12,14</p> <p>D16S539: 9,13</p> <p>D5S818: 8,9</p> <p>D7S820: 11,12</p> <p>TH01: 7,9,3</p> <p>TPOX: 11</p> <p>vWA: 16,19</p>
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 RF42977: Keith DE et al. Morphine activates opioid receptors without causing their rapid internalization. *J. Biol. Chem.* 271: 19021-19024, 1996 PubMed: 96324996
 RF50113: Louis N et al. Cloning and sequencing of the cellular-viral junctions from the human adenovirus type 5 transformed 293 cell line. *Virology* 233: 423-429, 1997 PubMed: 97360037

Propagation:	ATCC medium: Minimum essential medium Eagle with 2 mM L-glutamine and Earle's BSS adjusted to contain 1.5 g/L sodium bicarbonate, 0.1 mM non-essential amino acids, and 1.0 mM sodium pyruvate, 90% heat-inactivated horse serum, 10% Temperature: 37C
Related Products:	Recommended medium (without the additional supplements or serum described under ATCC Medium) — ATCC 30-2003 purified DNA 45504 purified DNA 45505 derivative CRL-10852
BioSafety:	Handle as potentially biohazardous material under at least Biosafety Level 2 containment.
BioSafety Level:	2

Required Forms:	These cells are distributed for research purposes only. The McMaster University releases the line subject to the following: 1) 293 cells or their products must not be distributed to third parties. Commercial interests are the exclusive property of the McMaster University. 2) Any proposed commercial use of these cells must first be negotiated with Microbix Biosystems Inc. [contact Kevin Koole], 341 Bering Avenue, Toronto, Ontario, Canada M8Z 3A8 Telephone: 416-234-1624, FAX: 416-234-1626, E-mail: customer.service@microbix.com , WWW: Microbix
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Revised :	Apr 24, 2001

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Questions or Comments?

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